ARTHROPOD REPELLENT PHARMACOPHORE MODELS, COMPOUNDS IDENTIFIED AS FITTING THE PHARMACOPHORE MODELS, AND METHODS OF MAKING AND USING THEREOF

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This invention was made by employees of the United States Army. The government has rights in the invention.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention generally relates to a pharmacophore for arthropod repelling activity. In particular, the present invention relates to a pharmacophore derived from compounds exhibiting arthropod repellent activities.

2. Description of the Related Art

Arthropods can expose one to disease vectors, inflict severe physiological stress, and their bites can be painfully distracting and lead to devastating secondary infections, entomophobia, dermatitis, and allergic reactions. Four of the most important parasitic diseases of humans are arthropod-borne. Of the 80 diseases important to military operations, more than two thirds are transmitted by arthropods. See Defense Intelligence Agency (1982) *Handbook of Diseases of Military Importance*. Washington, D.C.: Government Printing Office, 135. Such diseases include malaria, dengue fever, West Nile fever, sandfly fever, yellow fever, viral encephalitis, filariasis, Japanese encephalitis, rift valley fever, leishmaniasis, Bartonellosis, sleeping sickness, myliasis, plague, typhus, tick-borne relapsing fever, tularemia, rocky mountain spotted fever, Ehrlichiosis, scrub typhus, and the like.

Use of insect repellents is a vital countermeasure in reducing arthropod-related casualties. A repellent is a chemical that causes the insect to make oriented movement away from its source. See Dethier V G, et al. (1960) J. Econ. Entomol. 53:134-136. Repellents may be classified based on their site of application or their mode of action. The two important types of insect repellents are topical repellents and clothing repellents. Based on the mode of action, insect repellents can be further classified as vapor (or olfactory or spatial) repellents and contact (or gustatory) repellents. Repellents such as DEET, dimethyl phthalate, and ethyl hexanediol depend on their vapors to keep insects at a distance, but the contact repellents, such as Indalone, are slightly volatile so that the insect must touch the treated surface before being repelled. See Garson, L R and Winnike, M E (1968) J. Med. Entomol. 5:339-352; Kennedy, J S (1947) Bull. Entomol. Res. 37:593-607; and Kennedy, J S (1947) Bull. Entomol. Res. 37:593-607.

Throughout human history various repellents have been used. Turmeric (*Curcuma longa*, Family Zingiberaceae) in vegetable oil was used daily for protection against mosquitoes. See Philip, M I, et al. (1945) Indian Med. Gaz. 80:343-344. Anatto (*Bixa orellana*, Bixaceae) in vegetable or animal oil. See Mom, A M (1948) Rev. Argentina da Dermatosifilologia 32:303-306. Wormwood juice (*Artemisia absinthium*, Compositae) to repel gnats and fleas. See Arnold, W N (1989) Sci. Am. 260:112-117. Leaves and fruits of citron (*Citrus medica*, Rutaceae) to repel insects from stored clothing. See Rice, E L (1983) *Pest Control with Nature's Chemicals: Allelochemics and Pheromones in Gardening and Agriculture*. Norman, Okla.: University of Oklahoma Press. Sulfur was dusted on skin and clothing to repel chiggers. See Ewing, H E (1925) J. Econ. Entomol. 18:827-829. Application of a 1:10 solution of Epsom salts (hydrated calcium sulfate). See US Army Medical Field Service School (1933) *Essentials of Field Sanitation for the Medical Department, United States Army*. Carlisle Barracks, Penn: US Army Medical Field Service School. Pyrethrum (*Chrysanthemum cinerariaefolium*, Compositae) and citronella (*Cymbopogon nardus*, Gramineae). See Gupta, R K and Rutledge, L C (1994) Am. J. Trop. Med. Hyg. 50(Suppl):82-86.

The first synthetic repellents to gain wide acceptance were dimethyl phthalate and dibutyl phthalate. By the end of World War II, dimethyl phthalate, ethyl hexanediol (also called Rutgers 612), and Indalone (butyl-3,3-dihydro-2,2-dimethyl-4-oxo-2H-pyran-6-carboxylate) had been identified as superior mosquito repellents. See Stage, H H (1952) Mosquitoes. In: Stefferud A, ed. *Insects: The Yearbook of Agriculture*. Washington, D.C.: US Government Printing Office, 476-486. Unfortunately, in 1991 the US Environmental Protection Agency (EPA) canceled all registrations of ethyl hexanediol at the request of its manufacturers because of new information on possible adverse fetal developmental effects. See US Environmental Protection Agency (1991) 2-ethyl-1,3-hexanediol; receipt of requests to cancel. Fed. Reg. 8:4376-43768.

Perhaps the single most important event in the evolution of repellents was the discovery of DEET in 1954. See McCabe, E T, et al. (1954) J. Org. Chem. 9:493-498. DEET has virtually eclipsed other repellents for topical use, and remains the principal repellent in use today, more than 40 years after its discovery. Even though DEET is an effective repellent against a broad spectrum of arthropods, it has several drawbacks. Under warm, humid conditions, the application lasts for only 1 to 2 hours. DEET is a strong plasticizer, has a disagreeable odor, and feels "oily". DEET has been associated with allergic and toxic effects in some people, especially when used repeatedly on the skin in high concentrations. A report in 1976 showed regular applications of DEET on the skin of white rats was gonadotoxic and embryotoxic. See Gleiberman, S E, et al. (1976) Med. Parazitol. (Mosk). 45:65-69. DEET has been associated with bullous eruptions in the antecubital fossa and contact urticaria, and rare cases of toxic encephalopathy have occurred with excessive or prolonged use, particularly in infants and children. See Are insect repellents safe? *Lancet* (1988) 2:610-611. Use of DEET has been implicated in seizures among children.

Unfortunately, progress in the development of new repellents has been limited. One important reason for the lack of success in this area is the limited understanding of the repellents' mode of action on the target organisms. The general assumption that all repellents affect all arthropods in the same way is incorrect. It has been shown that even strains of the same species differ significantly in their tolerance to the same repellent. Therefore, selection of appropriate repellents for personal protection greatly depends on the species to be repelled. Also, a certain minimum effective evaporation rate of repellent is required to effectively repel insects. See Rutledge, L C, et al. (1986) Army Science Conference Proceedings 3:343-357.

Thus, a need exists for more effective repellents having less side-effects and methods for screening candidate compounds for repellent activity.

SUMMARY OF THE INVENTION

The present invention generally relates to a pharmacophore model for arthropod repellent activity.